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Glycemic control in children with type 1 diabetes: Insulin pump therapy versus multiple daily injections

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ABSTRACT

While many studies compared multiple daily injections (MDI) and insulin pump therapy on various clinical outcomes, the results remain inconclusive. This multicenter retrospective cohort study included 175 patients and aimed to evaluate the effects of different insulin therapy methods on various clinical outcomes, including hemoglobin A1c (HbA1c), total daily insulin dosage, body mass index, glomerular filtration rate, in pediatric patients with type 1 diabetes. In a linear mixed-effects regression analysis, a statistically significant interaction between time and treatment type on HbA1c was found. It suggested significantly higher reduction of HbA1c values between 12-month visit and baseline in the group receiving MDIs compared to insulin pump therapy. Patients using MDIs observed higher reduction of HbA1c levels and lower total daily insulin dose relative to insulin pump therapy group. Other changes of clinical indicators were the same for group of patients. Various studies report controversial results on long term effects of these treatments on HbA1c values necessitating large population-based cohort studies in this field.

Keywords: type 1 diabetes mellitus, insulin pump therapy, multiple daily injections, degludec, long-acting insulin, short-acting insulins, HbA1c

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases among children in Kazakhstan and worldwide with around 8.75 million globally affected individuals. According to claims data from the Unified National Electronic Health System of Kazakhstan, T1DM incidence rate accounted for 22.5 per 100,000 population at risk throughout 2014-2021 [1]. During the same time period, authors demonstrated the prevalence rate of patients diagnosed with T1DM at age between zero to 18 years accounting for 116 per 100,000 population in Kazakhstan. Concerning all-cause mortality, a study utilizing the mentioned data source demonstrated mortality rate 0.32 per 100,000 population at risk with infants aged up to 12 months and children with various complications having worse survival.

Several acute and long-term complications resulting from unregulated blood sugar levels among children diagnosed with T1DM can negatively affect various circulatory and metabolic processes potentially leading to delayed physical development [2, 3]. The most prevalent complications, which affect each third child with T1DM during the first three months after diagnosis, include lipodystrophy, hypoglycemia, and ketoacidosis [4]. These complications additionally exacerbate insulin absorption and lead to nephropathy, neuropathy, and retinopathy in the long term. Therefore, to prevent micro- and macro-vascular complications it is crucial to maintain stringent glycemic control [5].

Insulin therapy for children diagnosed with T1DM is a crucial part of their treatment. It includes various insulin medications, pens, or pumps and aims to mimic natural physiological insulin secretion [6, 7]. Multiple daily injections (MDIs) and continuous subcutaneous insulin infusion (CSII) are common insulin therapy delivery methods. Both mentioned treatment regimens closely emulate the natural pattern of insulin secretion [8].

MDIs, also known as basal bolus therapy, involves MDIs of rapid-acting insulin before meals, along with a prolonged-acting basal insulin [9]. Modern pharmaceutical products used for MDI provide a stable and exceptionally long duration of action, minimizing fluctuations in glucose-lowering activity over a 24-hour daily dosing period [10]. CSII, also referred to as insulin pump therapy, involves the use of a small electronic device to deliver a continuous supply of insulin into the body throughout the day, typically utilizing only rapid-acting insulin.

CSII better simulates natural insulin release patterns, potentially enhancing metabolic regulation [11, 12]. Some studies report improvements in patients' quality of life associated with CSII use [13]. The carbohydrate counting procedure, which involves calculating the carbohydrate content of a meal and adjusting the injected fast-acting insulin, accordingly, is utilized in MDI and requires high diabetes knowledge from patients. However, proper implementation of the carbohydrate counting method enables flexibility in meal selection and timing that is appropriate for a specific lifestyle [14]. Many studies indicate that CSII outperforms MDI in metabolic control because MDI is unable to adapt therapy to immediate changes in blood glucose [13, 15, 16]. Specifically, while these investigations suggest a significant reduction in hemoglobin A1c (HbA1c) levels among patients treated with CSII compared to MDI therapy, a number of studies demonstrate no significant differences in metabolic control outcomes between these treatment options, especially in the long term [17, 18].

Ongoing uncertainty persists regarding the potential differences between MDI and CSII insulin therapy methods regarding various clinical and metabolic outcomes of pediatric patients with T1DM. Therefore, the current study attempts to address this issue using data that include physical, clinical, and metabolic parameters of pediatric T1DM patients collected from various regions of Kazakhstan.

MATERIALS & METHODS

Study Design & Population

This multicenter retrospective cohort study includes children with T1DM in pediatric hospitals from three different regions of Kazakhstan (Aktobe, Astana, & Shymkent cities) during a period of 2022-2023. Thus, sampling frame included patients who were admitted to one of three endocrinology departments in pediatric hospitals with the diagnosis of T1DM to receive medical care during the one year of observation. Convenient sampling method were applied to get sufficient data. Inclusion criteria encompass having a clinically diagnosed type 1 diabetes, being between three and 18 years old, receiving intensive insulin therapy administered either via an insulin pump or through basal insulin injections, defined as four or more insulin injections per day. Additionally, only patients with at least one year of diabetes duration were considered for inclusion. A total of 591 patients were admitted to endocrinology departments of pediatric hospitals during the specified period. Patients without complete follow-up information, patients younger than three years at diagnosis and those who were 18 years or older; those who have diabetes duration less than one year; those who have been using three or fewer daily insulin injections; or individuals who used long-acting insulin in conjunction with CSII were not included. Out of 591 patients, 416 patients were excluded due to inconsistency with inclusion criteria. Participant selection process is shown in **Figure 1**. Vast majority of medical records did not contain follow-up information after six and 12 months of treatment. Specifically, laboratory findings like HbA1c, creatinine levels or anthropometric data were missing. Thus, these subjects were excluded.

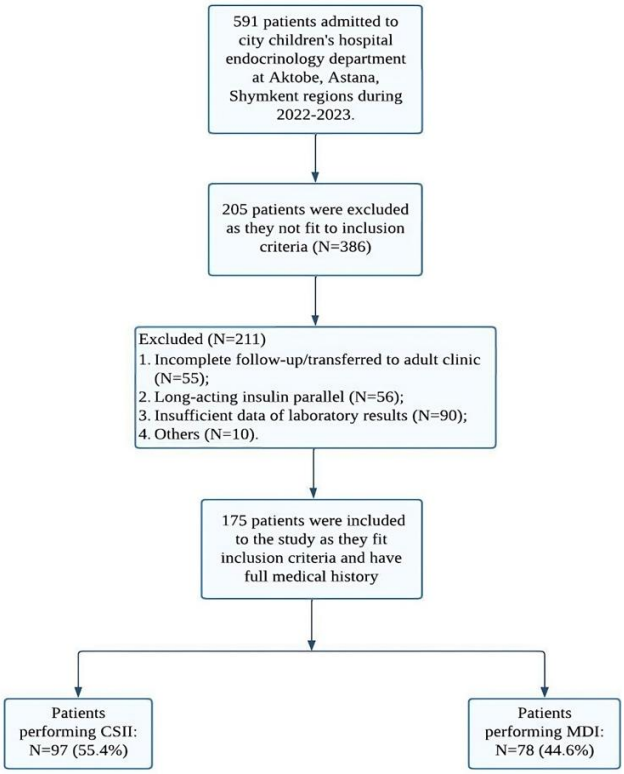

Figure 1. Flow-chart on participants' selection process (Source: Authors' own elaboration)

Study Interventions

All patients receiving CSII are those who were transferred from MDI to CSII before inclusion in the study. Medtronic Paradigm Veo MMT-754 insulin pump with rapid-acting insulin analogues was used in 97 cases. All these patients received one of the following medications: lispro (Humalog, Lilly, Indianapolis, IN, USA), aspart insulin (Novorapid, NovoNordisk, Bagsværd, Denmark) or glulisine (Apidra, Sanofi, Paris, France). Participants undergoing insulin therapy using MDI (N=78) had been receiving degludec (Tresiba, NovoNordisk, Bagsværd, Denmark) as their basal insulin, along with one of the short-acting insulins, such as lispro, aspart, or glulisine.

Follow-Up & Measurements

Data were collected from medical records at baseline and during two follow-up visits at six months and 12 months. It included various characteristics, such as sex, age, weight, height, body mass index (BMI), duration of diabetes and comorbidities. Variable assessing presence of comorbidities included the categories of no comorbidities, thyroid dysfunction, and other comorbidities, which encompassed diseases such as gastritis, anemia, psoriasis, and secondary cardiomyopathy. These variables were considered as potential confounders, while main exposure variable was insulin delivery method, represented by either receiving MDI or CSII. Primary outcome variable in this study was HbA1c levels (%), and secondary outcome measures included BMI, total daily dose of

Table 1. Descriptive analysis of socio-demographics & independent variables

Variable	Insulin therapy method		p-value
	CSII (n=97)	MDI (n=78)	
Age in years, mean±SD	11.57±4.07	11.62±4.12	0.938
Sex, n (%)			
Male	43 (44.3%)	37 (47.4%)	0.682
Female	54 (55.7%)	41 (52.6%)	
Diabetes duration in years, median (IQR)	3 (2-5)	3 (2-4)	0.083
Comorbidities, n (%)			
Absence	80 (82.5%)	56 (71.8%)	0.064
Thyroid dysfunction	8 (10.3%)	6 (7.7%)	
Other	9 (9.3%)	16 (20.5%)	

Table 2. Mean outcome measures by insulin therapy method & time

Outcome measure	Insulin therapy method					
	CSII			MDI		
	Baseline	Six months	12 months	Baseline	Six months	12 months
HbA1c, mean±SD	9.5±2.66	8.2±1.72*	7.9±1.25*	10.0±2.42	8.5±1.75*	7.9±1.24*
BMI, mean±SD	18.3±3.52	18.9±3.20*	19.4±2.90*	18.3±3.49	18.9±3.10*	19.5±2.80*
TDD, mean±SD	29.1±13.10	27.6±13.30*	29.2±13.30	29.0±12.00	27.2±11.60*	28.3±11.20
GFR, mean±SD	88.7±25.10	93.3±28.50	91.5±28.50	89.2±20.44	92.2±30.62	93.8±26.60

Note.*p<0.05 (using paired t-test with Tukey's correction pre- vs. post-sessions)

insulin (TDD) measured in IU/kg/day and glomerular filtration rate (GFR) measured in mL/min. Outcome variables were collected at baseline and during follow-up visits.

Statistical Analysis

Descriptive analysis summarized categorical variables using frequencies and relative frequencies, while numeric variables were analyzed using mean and standard deviation or median and interquartile range. The significance level for all statistical tests was set at 0.05 with a corresponding 95% confidence level. Bivariate analysis compared mean outcome values (BMI, HbA1c, GFR, and TDD) between the six-month visit and baseline, as well as between the 12-month visit and baseline. This was conducted separately for CSII and MDI groups using paired t-tests with Tukey's correction. The rationale for using this test includes the presence of three dependent groups introduced by baseline and two follow-up visits, the necessity to estimate the change over time within each treatment group, and the requirement to adjust for alpha inflation introduced by several pairwise comparisons. Within each of the two treatment groups, two pairwise comparisons were performed for each outcome: the six-month visit versus baseline and the 12-month visit versus baseline. Normal distribution assumptions for the outcome variables were checked using histograms, skewness measures, and the Shapiro-Wilk test. To account for within-subject correlation, a linear mixed-effects regression model was employed. This statistical approach was chosen for its flexibility in handling missing values and unbalanced data, as well as its ability to model both within-subject and between-subject variability. Additionally, it allows for adjusting for the confounding effects of other covariates. Treatment, time, and the interaction between treatment and time were fixed effects, with each participant included as random effects through the introduction of a random intercept. Unadjusted models for predicting mean outcome values included only treatment, time, and the interaction between treatment and time. In multivariate models, other covariates, such as age, sex, diabetes duration, and the presence of comorbidities, were added to control for confounding effects. The main focus was on the significance of interaction terms, indicating differences between the effects of CSII and MDI treatments on outcome variables over time. Adjusted predicted mean values of each outcome with a 95% confidence interval (CI) were plotted by treatment type and time point.

RESULTS

The study sample included 175 patients with T1DM, of whom 97 (55.4%) received insulin therapy using CSII, and MDI treatment was administered to 78 patients (44.6%). There were no statistically significant differences between treatment groups regarding participants' age and sex. The average age was 11.57 years (standard deviation [SD]=4.07) in CSII group and 11.62 years (SD=4.12) in MDI group (**Table 1**). More than half of the patients were females. Participants in both groups had a median diabetes duration of three years, with slightly more variability in CSII group, represented by a larger interquartile range and an outlying observation with 12 years of diabetes duration. In CSII group, 19.6% of participants had comorbidities, such as thyroid dysfunction and other endocrine and nonendocrine conditions, while in MDI group, 28.2% were found to have these comorbid conditions.

The results of paired t-tests with Tukey's correction for pairwise comparison of mean HbA1c, BMI, TDD, and GFR values between the visit after six months from the beginning of the follow-up and baseline, as well as between the 12-month visit and baseline, are presented in **Table 2**. Despite average HbA1c levels accounting for 9.5% (SD=2.66) in CSII group and 10.0% (SD=2.42) in MDI group, after one year of follow-up, the measurements averaged at 7.9% in both groups. Mean BMI values increased from 18.3 kg/m^2 (SD=3.5) at baseline to 19.4 kg/m^2 (SD=2.9) at the 12-month visit in CSII group, with comparable changes in MDI group during the same follow-up period, from 18.3 kg/m^2 (SD=3.5) to 19.5 kg/m^2 (SD=2.8). TDD significantly decreased from baseline to the six-month visit in both groups, leveling off at the 12-month visit. While mean GFR values tended to increase in both treatment groups, the changes were not statistically significant.

Table 3. Linear mixed-effects models assessing difference in effects between CSII & MDI groups on outcome variables over time

Factor	Univariate models		Multivariate models*	
	Coefficient (95%)	p-value	Coefficient (95%)	p-value
HbA1c				
Treatment group		0.064		0.066
CSII	Reference		Reference	
MDI	-0.54 (-1.10; 0.03)		-0.52 (-1.10; 0.03)	
Time				
Baseline	Reference	Reference	Reference	Reference
Six months	-1.49 (-1.80; -1.20)	<0.001	-1.49 (-1.80; -1.20)	<0.001
12 months	-2.09 (-2.40; -1.80)	<0.001	-2.08 (-2.40; -1.80)	<0.001
Treatment×time				
MDI*baseline	Reference	Reference	Reference	Reference
CSII*six months	0.24 (-0.18; 0.67)	0.260	0.24 (-0.20; 0.70)	0.258
CSII*12 months	0.48 (0.05; 0.90)	0.027	0.48 (0.05; 0.90)	0.027
BMI				
Treatment group		0.985		0.782
CSII	Reference		Reference	
MDI	0.01 (-0.90; 1.00)		0.18 (-0.70; 0.90)	
Time				
Baseline	Reference	Reference	Reference	Reference
Six months	0.66 (0.50; 0.90)	<0.001	0.66 (0.50; 0.90)	<0.001
12 months	1.21 (1.00; 1.40)	<0.001	1.21 (1.00; 1.40)	<0.001
Treatment×time				
MDI*baseline	Reference	Reference	Reference	Reference
CSII*six months	-0.02 (-0.30; 0.30)	0.914	-0.02 (-0.30; 0.30)	0.914
CSII*12 months	-0.05 (-0.30; 0.20)	0.707	-0.05 (-0.30; 0.20)	0.707
TDD				
Treatment group		0.933		0.967
CSII	Reference		Reference	
MDI	0.16 (-3.60; 3.90)		-0.05 (-2.60; 2.50)	
Time				
Baseline	Reference	Reference	Reference	Reference
Six months	-1.83 (-2.50; -1.10)	<0.001	-1.83 (-2.50; -1.10)	<0.001
12 months	-0.68 (-1.40; -0.004)	0.051	-0.61 (-1.40; 0.004)	0.051
Treatment×time				
MDI*baseline	Reference	Reference	Reference	Reference
CSII*six months	0.34 (-0.60; 1.30)	0.463	0.34 (-0.60; 1.30)	0.463
CSII*12 months	0.79 (-0.10; 1.70)	0.093	0.79 (-0.10; 1.70)	0.093
GFR				
Treatment group		0.819		0.891
CSII	Reference		Reference	
MDI	0.95 (-7.20; 9.10)		1.0 (-6.40; 8.40)	
Time				
Baseline	Reference	Reference	Reference	Reference
Six months	3.24 (-2.90; 9.40)	0.303	3.29 (-2.88; 9.48)	0.295
12 months	5.22 (-1.00; 11.40)	0.098	5.23 (-0.97; 11.43)	0.098
Treatment×time				
MDI*baseline	Reference	Reference	Reference	Reference
CSII*six months	1.00 (-7.30; 9.20)	0.821	0.76 (-7.50; 9.10)	0.857
CSII*12 months	-3.60 (-11.90; 4.60)	0.388	-3.66 (-11.90; 4.60)	0.387

Note. *Multivariable model is adjusted for age, sex, diabetes duration, & comorbidities

Linear mixed-effects regression modeling was employed to assess changes in the outcome variables between treatment groups over time (**Table 3**). In the multivariate model predicting HbA1c levels, there was a borderline significant effect of treatment (p=0.066) and a significant effect of time (p<0.001) after adjustment for other covariates.

Individuals in CSII group had, on average, lower HbA1c values compared to MDI group (adjusted coefficient -0.52, 95% CI: -1.1; 0.03). At the six-month and 12-month visits, participants overall had lower mean HbA1c values compared to baseline (**Figure 2**). A significant interaction was found between treatment and the 12-month time point (adjusted coefficient 0.48, 95% CI: 0.05; 0.9).

The multivariate model fitted to predict BMI suggests a significant time effect (p<0.001), no treatment effect, and no significant interaction between treatment and time. The results suggest that, on average, patients had higher BMI after six and 12 months compared to baseline, with adjusted coefficients of 0.66 (95% CI: 0.5; 0.9) and 1.21 (95% CI: 1.0; 1.4). Similarly, only a significant time effect was found in a multivariate model predicting the total daily dosage. Finally, GFR values were associated with neither treatment, nor time, nor interaction with treatment and time. **Appendix A** shows results of two-way repeated measures analysis of variance.

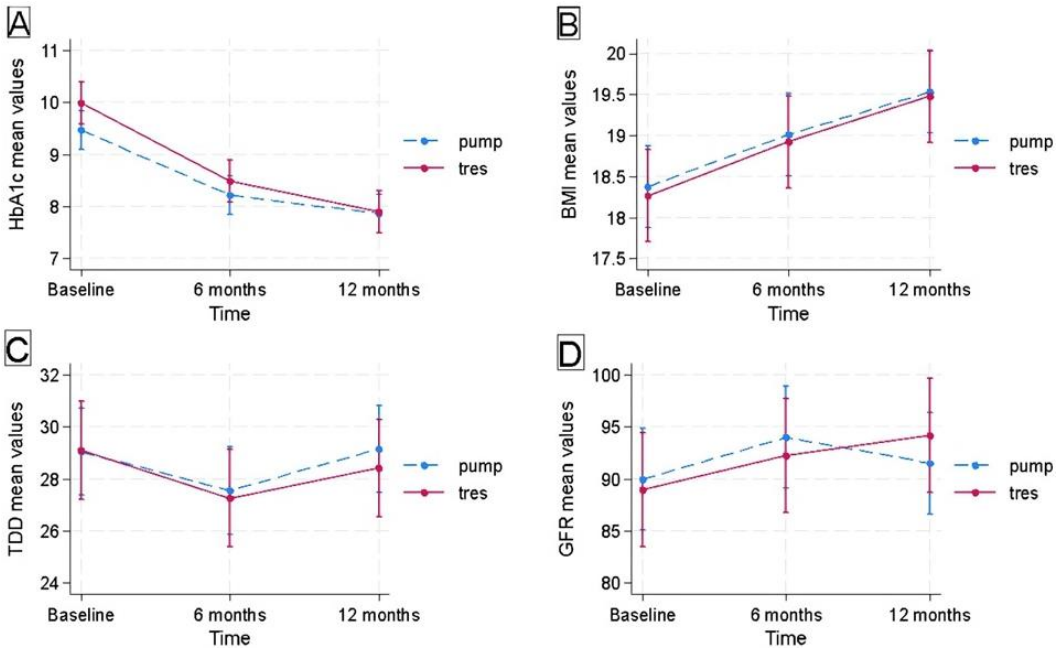

Figure 2. Adjusted predictions of HbA1c (A), BMI (B), TDD (C), & GFR (D) mean values by visit & treatment type with 95% CI (Source: Authors' own elaboration)

DISCUSSION

In this multicenter retrospective cohort study, patients with T1DM were longitudinally monitored and their clinical outcomes were contrasted by insulin delivery regimens. Patients in both treatment groups initially had persistent glucose control issues, indicated by baseline mean HbA1c levels of 9.5% and 10.0% in CSII and MDI group, respectively.

While they experienced favorable changes in their HbA1c levels after 12 months, a higher reduction of HbA1c values between 12-month visit and baseline was observed in MDI group compared to patients in CSII treatment (-2.1% vs. -1.6%, respectively). This indicates a more profound effect in glycemic control for insulin therapy using MDI.

While some studies [19, 20] demonstrate a significantly more reduction in HbA1c values in patients receiving CSII along with better symptom control compared to MDI, other studies [14] indicate no significant differences. Several studies also suggest that employing a combination of CSII and continuous glucose monitoring results in better HbA1c management compared to MDI coupled with self-monitoring of blood glucose [21]. Some of these studies examined metabolic control in the same patient group both before and after CSII therapy [5], while other investigations compared distinct patient groups undergoing CSII or MDI treatment, which was similar to our study [18].

Meta-analysis conducted by [15] (40 studies including, 1,110 patients on CSII and 1,142 patients on either conventional or basal bolus MDI with mean trial duration of 53 weeks) and another meta-analysis by [22] (25 trials enrolled 1,456 adults with a mean age of 40.4 years, and 543 children with a mean age of 8.3 years) revealed a notable reduction in HbA1c level in both children and adults undergoing CSII treatment as opposed to MDI. In a study conducted by [18], a total of 144 cases received CSII and MDI were administered to 149 patients as a part of a randomized controlled trial (RCT). The results indicated no significant difference in HbA1c values between two groups during a one-year follow-up. Also, a recent longitudinal study assessing the two insulin regimens in children with T1DM reported that there was no noteworthy distinction between CSII and MDI [14]. There was no previous study that reported findings with similar results. We suggest that this contradiction might be explained by the fact that the effectiveness of insulin pumps depends on various factors such as insulin sensitivity (some individuals may find that they are more sensitive to insulin delivered via MDI compared to insulin delivered through a pump), lifestyle, diet, exercise habits, and overall health. Additionally, CSII method requires proper pump settings, infusion site management, and good training in pump management, whereas injection therapy is much simpler and more convenient to use. It eliminates the risk of technical malfunctions, which are likely to arise during the first year of pump utilization. Moreover, MDI therapy involves injections of both basal (long-acting) and bolus (short-acting) insulins multiple times a day. This method can provide a more consistent insulin delivery compared to insulin pumps, which use only rapid acting insulin types. Therefore, individuals using insulin pumps need to adjust their basal rates to match their individual insulin needs, which can vary depending on factors such as physical activity, stress, illness, and hormonal changes. Another explanation for the observed controversial findings might be that in other studies, a combination of CSII and continuous glucose monitoring was utilized. This combination could have contributed to a significant reduction in HbA1c levels, unlike the sole use of CSII as in our study [23-25]. Moreover, the use of different insulin pump models and generations may also result in varying effectiveness in diabetes management. In our study, participants used Medtronic Paradigm Veo MMT-754, but differences in maintaining glycemic control might exist across different devices used for CSII [26, 27].

Treatment effect on HbA1c levels, indicated by a p-value of 0.066, warrants careful consideration and critical discussion since p-values are influenced by sample size, study design, variability within the data, and other factors. Therefore, it

should be complemented by a thorough examination of effect sizes, clinical relevance, and the context in future studies.

In a current study, both groups experienced a gradual increase of BMI levels over the 12-month period. These results are comparable to other studies that report an increase in BMI in both CSII and MDI groups [28, 29]. However, some studies indicate a gradual reduction in average BMI values as well [30, 31]. Therefore, there is controversy concerning the effects of CSII and MDI therapy on BMI [32, 33]. Also, prior research examining the impact of various insulin regimens on weight gain has yielded inconclusive results [34-36].

Comprehensive prospective studies are essential in this regard to explore how the utilization of various insulin regimens affects weight and other anthropometric measures.

We also observed an increase in GFR levels among patients in both groups after a 12-month period. This could be a compensatory response to hyperglycemia and the commonly observed increased renal blood flow in patients with diabetes, a phenomenon known as hyperfiltration. Although various methods of insulin therapy may not directly impact GFR, they potentially exert an indirect influence by achieving good glycemic control and reducing HbA1c levels [37].

Given study also found a trend for having a lower TDD after a year of follow-up in patients on MDI compared to insulin pump patients, which contradicts previous studies [6]. The possible explanation why children, who receive MDI therapy, achieve lower TDD compared to those on CSII might be site rotation in MDI therapy, which might contribute to better insulin absorption. An additional factor associated with MDI therapy that might lead to more effective insulin delivery is a possibility to administer precise bolus doses before meals. However, determinants of TDD are multifaceted and can include numerous factors, such as lifestyle, insulin sensitivity, and individual response. Therefore, more research in this direction should be conducted.

Current study has several strengths. Firstly, usage of primary medical records minimizes recall bias. Secondly, this research is the first study in Central Asian region on identifying differences between MDIs and insulin pump therapy. Since this is a multi-center study, results are expected to be generalizable for a wider population. Another notable aspect of this study lies in its examination of real-world outcomes within a population-based cohort over an extended period, distinguishing it from previous research. While not conducted as an RCT, it provides valuable insights into the long-term effects, contrasting with smaller-scale pediatric studies that typically feature limited patient samples, shorter observation periods. Several limitations should be considered as well. Specifically, a nonrandomized design used in this study might have led to decreased internal validity of the study findings due to possible selection bias. This could have potentially distorted the observed differences in outcome measures between two insulin therapy methods. Also, despite that BMI is a valid anthropometric measure, BMI standard deviation scores (BMI-SDS) might have been more appropriate to use in this study to assess a child's physical growth. The study lacked sufficient data concerning diabetic ketoacidosis and hypoglycemic episodes. Thus, these parameters could not be analyzed in the current investigation. Another limitation is missing data. As the data in medical records was not designed for the present study, incomplete records were anticipated.

In this multicenter cohort study of children with T1DM we evaluated the effectiveness of MDI and CSII on glycemic control and other clinical parameters using real-world data. Insulin therapy utilizing MDI with degludec demonstrated better glycemic outcomes compared to insulin pump therapy with fast-acting. These findings underscore the importance of considering individualized treatment approaches in diabetes management. This study offers several critical learning points that contribute to our understanding of differences between two insulin delivery methods. The findings of this study have practical implications for clinical practice and healthcare policy. Healthcare providers can utilize the insights gained to optimize treatment strategies, improve patient outcomes, and enhance the quality-of-care delivery for T1DM patients. By analyzing a population-based cohort over an extended duration, this study provides valuable insights into the real-world outcomes of CSII and MDI. The inclusion of a diverse and sizable population enhances the generalizability of the findings to broader clinical contexts. While insulin pumps are widely recognized for their benefits, our study suggests that certain patient populations may derive optimal glycemic outcomes through MDI. Further research is warranted to explore the factors contributing to this observed difference and to refine personalized treatment strategies for individuals with diabetes.

Author contributions: AD & GS: conceptualization & writing–review & editing; **AD & AG:** supervision; **AD, GZ, AI, AN, AU, & AN:** methodology; **GS:** writing–original draft preparation; **AG:** software, visualization, & formal analysis; **GZ & AG:** validation; **MR:** investigation; **AA:** resources; **MR, GZ, KF, MK, & MS:** data curation; **MK:** project administration; **MS & AN:** funding acquisition. All authors have agreed with the results and conclusions.

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Ethical statement: The authors stated that the study was conducted in accordance with the Declaration of Helsinki & approved by University Medical Center Institutional Research Ethics Board on 1 July 2023, protocol code 01-011. Written informed consents were obtained from the participants.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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APPENDIX A

Table A1. Results of two-way repeated measures analysis of variance

Source	SS	df	MS	F-value	p-value
HbA1c					
Treatment	11.360	1	11.360	1.26	0.263
Time	310.770	2	155.390	155.19	<0.001
Treatment#time	4.780	2	2.390	2.39	0.094
Subject/treatment	1,534.370	170	9.010		
Error	334.430	334	1.000		
Total	2,188.190	509			
BMI					
Treatment	0.025	1	0.025	0.00	0.977
Time	121.680	2	60.840	134.66	<0.001
Treatment#time	0.067	2	0.034	0.07	0.928
Subject/treatment	5,115.750	173	29.570		
Error	156.330	346	0.450		
Total	5,394.690	524			
TDD					
Treatment	37.190	1	37.190	0.08	0.777
Time	272.970	2	136.480	28.42	<0.001
Treatment#time	13.490	2	6.740	1.40	0.247
Subject/treatment	79,694.960	173	460.660		
Error	1,661.840	346	4.800		
Total	81,682.700	524			
GFR					
Treatment	3.380	1	3.380	0.00	0.962
Time	1,627.260	2	813.630	2.12	0.121
Treatment#time	633.250	2	316.620	0.83	0.438
Subject/treatment	254,798.810	173	1,472.830		
Error	131,342.300	343	382.920		
Total	387,564.900	521			

Note. *Sources of variation: treatment-treatment variable: CSII & MDI groups; time-time variable: Baseline & follow-up visits; treatment#time-interaction between treatment & time; subject/treatment-subject nested in treatment; error-residual variability; & total-total variability